HHS Public Access

Author manuscript

Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2014 September 01.

Published in final edited form as:

Pharmacoepidemiol Drug Saf. 2013 September ; 22(9): 1013–1018. doi:10.1002/pds.3495.

Medications in the First Trimester of Pregnancy: Most Common Exposures and Critical Gaps in Understanding Fetal Risk

Phoebe G. Thorpe, MD, MPH[1], **Suzanne M. Gilboa, PhD, MHS**[1], **Sonia Hernandez-Diaz, MD, DrPH**[2], **Jennifer Lind, PharmD, MPH**[1], **Janet D. Cragan, MD, MPH**[1], **Gerald Briggs, BPharm, FCCP**[3], **Sandra Kweder, MD**[4], **Jan M. Friedman, MD, PhD**[5], **Allen A. Mitchell, MD**[6], **Margaret A. Honein, PhD, MPH**[1], and **the National Birth Defects Prevention Study**

[1]Division of Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, San Francisco

[2]Harvard University School of Public Health San Francisco

[3]University of California, San Francisco, University of Southern California, Los Angeles, and Washington State University, Spokane

[4]Office of New Drugs at the Food and Drug Administration

[5]University of British Columbia

[6]Slone Epidemiology Center at Boston University

Abstract

Purpose—To determine which medications are most commonly used by women in the first trimester of pregnancy and identify the critical gaps in information about fetal risk for those medications.

Methods—Self-reported first-trimester medication use was assessed among women delivering liveborn infants without birth defects and serving as control-mothers in two large case-control studies of major birth defects. The Teratology Information System (TERIS) expert Advisory Board ratings of quality and quantity of data available to assess fetal risk were reviewed to identify information gaps.

Results—Responses from 5,381 mothers identified 54 different medication components used in the first trimester by at least 0.5% of pregnant women, including 31 prescription and 23 over-the-counter medications. The most commonly used prescription medication components reported were

Correspondence: Phoebe G. Thorpe, MD, MPH, CDC, 1600 Clifton Rd., MS-E86, Atlanta, GA 30333, Telephone: 404 498-3877 Fax: 404 498-3040 pht1@cdc.gov.

Conflict of Interest: SHD has been an advisor for Pregnancy Registries sponsored by Novartis and GSKBiologics, and has received training grants from Pfizer. Until August 2012, AAM owned over $20,000 in stock in Johnson & Johnson, which manufactures a number of products cited in this manuscript. Over the past two years, the Slone Birth Defects Study received contract support from GSK for an analysis involving bupropion; GSK had no role (or knowledge of) the current analysis. JMF writes the TERIS database but has no other potential conflicts of interest. The remaining authors have no potential conflicts of interest to report.

Disclaimer: The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Preliminary results presented as a poster at the 15th Annual National Birth Defects Prevention Network Meeting, Arlington, VA, February 27-29, 2012.

progestins from oral contraceptives, amoxicillin, progesterone, albuterol, promethazine, and estrogenic compounds. The most commonly used over-the-counter medication components reported were acetaminophen, ibuprofen, docusate, pseudoephedrine, aspirin, and naproxen. Among the 54 most commonly used medications, only two had 'Good to Excellent' data available to assess teratogenic risk in humans, based on the TERIS review.

Conclusions—For most medications commonly used in pregnancy, there are insufficient data available to characterize the fetal risk fully, limiting the opportunity for informed clinical decisions about the best management of acute and chronic disorders during pregnancy. Future research efforts should be directed at these critical knowledge gaps.

Keywords

medication; pregnancy; fetal risk; teratogen

Introduction

In the last three decades, use of medications during pregnancy has increased. In 2006-2008, over 90% of women reported using at least one prescription or over-the-counter medication during pregnancy, and over 80% reported use during the first trimester, a critical period of organogenesis.[1] Because pregnant women are typically excluded from clinical trials for new medications and animal findings may not predict human effects, the teratogenicity of new medications in humans is usually not well characterized at the time of initial marketing. Based on an analysis performed in 2011 using Teratology Information System (TERIS) expert reviews, among 172 medications approved for use in the United States between 2000-2010, 70% had no human data and 98% had insufficient published data to determine teratogenic risk in humans.[2] Prior analyses provided prevalence estimates for specific prescription[1] and over-the-counter medications;[3] we sought to update and extend this work by creating an updated list of the most commonly used medications in pregnancy and assessing the quantity and quality of information regarding teratogenic risks that is available to inform clinical decisions for these medications.

Methods

The pregnancy exposures for mothers of control-infants (liveborn infants with no major birth defects) from two large multi-site case-control studies, the Slone Epidemiology Center's Birth Defects Study (BDS) and the CDC-coordinated National Birth Defects Prevention Study (NBDPS), were used to estimate the prevalence of first trimester medication component use. Detailed methods for BDS and NBDPS have been described previously.[1] Briefly, both studies gather self-reported prescription and over-the-counter medication exposures via computer assisted telephone interviews that are designed to prompt recall for medication use and timing of use.[4] To update previously-described prescription and over-the-counter medication prevalence estimates,[1,3] we limited analyses to the most current 4-year time period of data available for control mothers in each study: births between January 1, 2006, and December 31, 2009, in BDS or those with an estimated due date between January 1, 2004, and December 31, 2007, in NBDPS. Because the studies have different timelines for conducting maternal interviews (BDS data are available sooner

than NBDPS data), the time periods available were not identical. The Slone Drug Dictionary (Boston University) was used to identify the individual components for each reported medication (e.g., use of acetaminophen with codeine counted as one exposure to acetaminophen and one exposure to codeine). We excluded medications used exclusively intravenously, locally (e.g., procaine), or topically, but included those used intra-vaginally. Medications reported by type but not by specific name (e.g., antibiotic, not otherwise specified) were excluded. Due to variability in preparations, vitamins, minerals, herbal supplements and vaccines were also excluded.

Prevalence of first trimester use of medication components was estimated for each study (BDS and NBDPS). We compared the prevalence estimates between the two studies and calculated a pooled estimate. Medication components reported by at least 0.5% of control-mothers in the first trimester of pregnancy based on the pooled data were defined as those most commonly used and were included in this analysis.

To obtain a rating of the quality and quantity of information available regarding human teratogenic risk for these frequently-used medication components, we searched the TERIS database.[5] TERIS rates the risk of permanent abnormality of structure or function in a child as a result of maternal exposure during pregnancy to commonly encountered doses of an agent. The rating is based on consensus of the TERIS authors and six internationally-recognized authorities in clinical teratology who comprise the TERIS Advisory Board. The assessment is made on the basis of the reproducibility, consistency, and biological plausibility of published clinical, epidemiological, and experimental data for each exposure. The TERIS summary also rates the available data on which the risk evaluation is based as *None*, *Limited*, *Fair*, *Good*, *Excellent*, or in an intermediate category, such as *Fair to Good*. Risk assessments based on evidence that is *Limited* or *Fair* are considered to be tentative and may change as more information becomes available. Even with *Good* data, only crude estimates of the magnitude of the risk are often possible. While the broader goal is to inform the fetal risk of medication exposure, we did not include the magnitude of risk from TERIS because the focus of this analysis is the existing gaps in available evidence for decision-making. We included the Food and Drug Administration (FDA) pregnancy category label (A, B, C, D, or X) of each prescription component.[6] These categories are assigned at the time of marketing approval and take into account both the available data on risks of various adverse reproductive outcomes (usually from animal studies) and the benefit of maternal treatment during pregnancy. However, they are not systematically updated on the basis of subsequent studies.[7] Because the FDA does not require pregnancy categories be published on product labels for over-the-counter medications, such information is not routinely available for clinical and individual decision making, and therefore was not included in this analysis.

Results

Responses from 5,381 mothers of infants without major birth defects were included: 1,923 from BDS and 3,458 from NBDPS. The prevalence estimates for each medication component varied little between the studies despite minor methodological differences and independent study populations (Table 1 and Table 2). Based on pooled prevalence estimates,

we found that 54 unique medication components were used by 0.5% or more of women in the first trimester of pregnancy: 23 over-the-counter and 31 prescription medication components. The most common types of medications included analgesics, laxatives, cough and cold remedies, oral contraceptives, antibiotics, antihistamines, asthma medications, and antacids. The most common specific prescription components included progestins from oral contraceptives, amoxicillin, progesterone, albuterol, promethazine and estrogenic compounds; over-the-counter components included acetaminophen, ibuprofen, docusate, pseudoephedrine, aspirin, and naproxen.

Based on the TERIS rating of the quantity and quality of data available to assess the teratogenic risk, 34 (63%) of these medication components had V*ery Limited to Fair* data, 18 (33%) had *Fair to Good* data, and 2 (4%) (promethazine and doxylamine) had G*ood to Excellent* data available (Tables 1 and 2). The 31 prescription medications used most commonly included 1 (3%) in FDA Pregnancy Category A, 9 (29%) in Category B, 12 (39%) in Category C, 2 (6%) in Category D, and 7 (23%) in Category X (Table 2).

Discussion

The reported prevalence, based on responses from control mothers from two large multi-site studies, represents the most robust contemporary estimate available for use of medications in the first trimester of pregnancy in the United States and provides a more current comprehensive listing of both prescription and over the counter medications. The prevalence estimates are quite similar in the two studies. When compared to estimates from previous analyses from these studies,[1,3] the ranking of medications has shifted slightly, likely reflecting changes in use that occur over time. This analysis also extends earlier work to address the critical gaps in our understanding of fetal risks. Based on the quality and quantity of available data assessed by TERIS, only 2 (4%) of the 54 most commonly used medications received a *Good to Excellent* rating of quality and quantity data available to assess teratogenic risk. Some exposures were likely inadvertent, such as use of progestins (presumably from failed contraceptive use) in early pregnancy. For the vast majority of the commonly used medications, insufficient data exist to characterize fully the fetal risk when used during pregnancy, limiting opportunities for informed clinical decisions about the best management of maternal conditions.[8]

Medication use during pregnancy is common and has increased approximately 68% over the past 30 years in the United States.[1] Factors potentially contributing to this trend include chronic health conditions associated with increased maternal age and the growing use of medication in the U.S. population.[9,10] Numerous health conditions such as infections, asthma, and depression may require treatment during pregnancy, but there is little guidance available to inform clinical practice. A recent American College of Obstetricians and Gynecologists (ACOG) committee opinion provided some guidance on use of antibiotics during pregnancy, but even for the medications cited improved data are needed to permit a more robust evaluation of the risk versus benefit for specific situations.[11]

While prescription medications are assigned an FDA pregnancy category as part of the FDA-approved label, these categories can be misinterpreted. For example, progestins found

in oral contraceptives are labeled as category X, presumably because they provide no clinical benefit as contraceptives during pregnancy. However, when these agents are inadvertently used in pregnancy, available data indicate that the teratogenic risk is small or non-existent.[8,12] The FDA is transitioning to a new, expanded labeling system that will provide improved information to women and their health care providers by including a description of the available data and what is known with regard to human teratogenic risk.[13] Despite this new labeling system, the insufficiency of data available remains a concern.

A potential limitation of our findings is that all medication exposures were self-reported after pregnancy by women who delivered liveborn infants without major birth defects. Women might underreport less memorable exposures or their reports may lack specificity among similar products (e.g., single component versus multi-component acetaminophen products), but the BDS and NBDPS studies are designed to maximize recall accuracy by specifically probing for medication use by indication and by named medications.[4] While limitations exist with self-reported data, analyses based solely on medical and pharmacy records do not capture over-the-counter medications, nor prescriptions that have been saved or borrowed from others.[14] Finally, the TERIS evaluation of the quality and quantity of available information is made by an expert advisory board, and the specific composition of the panel could influence their ratings and our findings.

The current study highlights the lack of available information regarding fetal safety for medications commonly used in pregnancy. While steps are being taken to improve clinical decision making by revising the FDA labeling to convey more detailed and specific information, significant evidence gaps exist in understanding the teratogenic risk of the vast majority of medications used in early pregnancy. While adequate evidence to inform every decision about every pregnancy might not be possible, addressing these critical gaps has the potential to improve both fetal and maternal health, and research efforts should be directed towards this goal.

Acknowledgement

Authors would like to acknowledge Lisa Mathis, MD, for her contribution to this work.

Role of the Sponsor: Employees of the Centers for Disease Control and Prevention supervised the design and conduct of the study, the analysis and interpretation of the data, and the preparation, review and approval of the manuscript.

Funding/Support: Drs. Hernandez-Diaz and Mitchell were supported by grant R01 HD046595 from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Dr. Mitchell also receives support through Cooperative Agreement no. U50/CCU113247 with the Centers for Disease Control and Prevention to the Slone Epidemiology Center through the Massachusetts Department of Public Health. This work was also supported through cooperative agreements under PA 96043, PA 02081 and FOA DD09-001 from the Centers for Disease Control and Prevention to the Centers for Birth Defects Research and Prevention participating in the National Birth Defects Prevention Study.

References

1. Mitchell AA, Gilboa SM, Werler MM, Kelley KE, Louik C, Hernandez-Diaz S, et al. Medication use during pregnancy, with particular focus on prescription drugs: 1976-2008. Am J Obstet Gynecol. 2011; 205(1):51–e1. [PubMed: 21514558]

2. Adam MP, Polifka JE, Friedman JM. Evolving knowledge of the teratogenicity of medications in human pregnancy. Am J Med Genet C Semin Med Genet. 2011; 157(3):175–82. [PubMed: 21766440]
3. Werler MW, Mitchell AA, Hernandez-Diaz S, Honein MA, et al. Use of over-the-counter medications during pregnancy. Am J Obstet Gynecol. 2005; 193:771–7. [PubMed: 16150273]
4. Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. Am J Epidemiol. Apr; 1986 123(4):670–6. [PubMed: 3953545]
5. Friedman, JM.; Polifka, JE. Micromedex Reproductive Risk Information System (REPRORISK). Thomson MICROMEDEX; Englewood, Colorado: 2011. TERIS.
6. [accessed 15 May 2012] FDA product labels accessed for pregnancy categories at Dailymed. http://dailymed.nlm.nih.gov/dailymed/about.cfm
7. Federal Register. Office of the Federal Register, National Archives and Records Administration. Washington, DC: 1979.
8. Lo WY, Friedman JM. Teratogenicity of recently introduced medications in human pregnancy. Obstet Gynecol. 2002; 100(3):465–73. [PubMed: 12220765]
9. Ahluwalia IB, Mack KA, Mokdad A. Report from the CDC. Changes in selected chronic disease-related risks and health conditions for nonpregnant women 18-44 years old BRFSS. J Womens Health (Larchmt). 2005; 14(5):382–6. [PubMed: 15989409]
10. Wysowski DK, Governale LA, Swann J. Trends in outpatient prescription drug use and related costs in the US: 1998-2003. Pharmacoeconomics. 2006; 24(3):233–6. [PubMed: 16519545]
11. American College of Obstretricians and Gynecologists Committee on Obstetric Practices. Obstet Gynecol. 2011; 117(6):1484–5. ACOG Committee Opinion No. 494: Sulfonamides, nitrofurantoin, and risk of birth defects. [PubMed: 21606771]
12. Briggs, GB.; Freeman, RK.; Sumner, JY., editors. Drugs in Pregnancy and Lactation. 9th Ed. Lippincott Williams & Wilkins; Philadelphia, PA: 2011.
13. Kweder SL. Drugs and biologics in pregnancy and breastfeeding: FDA in the 21st century. Birth Defects Res A Clin Mol Teratol. 2008; 82(9):605–9. [PubMed: 18704917]
14. Petersen EE, Rasmussen SA, Daniel KL, Yazdy MM, Honein MA. Prescription medication borrowing and sharing among women of reproductive age. J Womens Health (Larchmt). 2008; 17(7):1073–80. [PubMed: 18774892]

Key points

1. This report updates the list of the most commonly used medications in the first trimester of pregnancy in the United States.
2. Teratogenic risk of the most commonly used medications has not been adequately studied in human pregnancy.
3. Improved understanding of the fetal risk associated with medication use during pregnancy could better inform clinical decisions regarding treatment.

Table 1

Commonly used over-the-counter medication components* in the first trimester of pregnancy and their TERIS** data ratings, the Slone Epidemiology Center's Birth Defects Study (BDS) (2006-2009) and the National Birth Defects Prevention Study (NBDPS) (2004-2007)

	Percent reporting use			
Over-the-counter medication components	BDS (N=1923)	NBDPS (N=3458)	Pooled (N=5381)	TERIS Data Rating**
Acetaminophen	55.2	56.1	55.8	Fair to Good
Ibuprofen	26.3	21.9	23.5	Fair to Good
Docusate	4.8	8.7	7.3	Fair
Pseudoephedrine	5.7	6.8	6.4	Fair
Aspirin	8.1	3.7	5.3	Good
Naproxen	5.1	3.9	4.3	Limited to Fair
Diphenhydramine	5.9	2.3	3.6	Fair
Loratadine	4.7	2.8	3.4	Fair
Dextromethorphan	2.1	3.3	2.9	Limited to Fair
Guaifenesin	2.6	2.1	2.3	Fair
Cetirizine	2.3	1.5	1.8	Limited to Fair
Doxylamine	1.2	2.1	1.8	Good to Excellent
Bismuth Subsalicylate	4.0	0.4	1.6	Limited
Chlorpheniramine	0.7	1.8	1.4	Fair to Good
Fexofenadine	1.3	1.4	1.4	Very Limited
Phenylephrine	2.2	0.7	1.3	Fair to Good
Ranitidine	1.6	0.4	0.9	Fair to Good
Miconazole	1.6	0.3	0.7	Fair
Famotidine	1.3	0.3	0.7	Limited to Fair
Simethicone	0.8	0.5	0.6	Very Limited
Psyllium	1.3	0.2	0.6	Limited to Fair
Omeprazole	0.8	0.4	0.5	Fair to Good
Oxymetazoline	0.9	0.2	0.5	Limited to Fair

* Varying strengths of the same component were combined. Commonly used was defined as exposure to any component in the first trimester as reported by 0.5% or more women. Multiple exposures to the same component in the first trimester were counted only once.

** Teratology Information System (TERIS) - The data available on which the risk assessment is based is rated as *None, Limited, Fair, Good*, or *Excellent*. Risk assessments based on evidence that is *Limited* or *Fair* ought to be considered tentative and may change as more information becomes available. Even with *Good* data, only crude estimates of the magnitude of the risk are often possible. Each agent is based on a consensus of ratings by seven internationally-recognized authorities in clinical teratology.

Table 2

The most commonly used prescription medication components* in the first trimester of pregnancy, their Food and Drug Administration (FDA) pregnancy categories and TERIS** data ratings, Slone Epidemiology Center's Birth Defects Study (BDS) (2006-2009) and the National Birth Defects Prevention Study (NBDPS) (2004-2007)

	Percent reporting use			FDA	
Prescription medication components	BDS (N=1923)	NBDPS (N=3458)	Pooled (N=5381)	Pregnancy Category	TERIS Data Rating**
Progestins[a]	5.2	4.4	4.7	X	Good
Amoxicillin	2.3	4.6	3.8	B	Good
Progesterone	4.2	2.9	3.4	X	Good
Albuterol	4.2	2.8	3.3	C	Limited
Promethazine	0.8	4.3	3.1	C	Good to Excellent
Estrogenic compounds[b]	2.9	3.0	2.9	X	Good
Levothyroxine	3.8	2.3	2.8	A	Fair
Ondansetron	3.7	2.1	2.7	B	Limited
Azithromycin	2.2	1.7	1.9	B	Limited to Fair
Clomiphene	1.3	2.0	1.8	X	Fair to Good
Sertraline	1.2	1.7	1.5	C	Fair
Fluticasone	2.0	1.2	1.5	C	Limited to Fair
Follitropin[c]	2.6	0.9	1.4	X	Very Limited
Hydrocodone	1.4	1.3	1.3	C	Limited
Nitrofurantoin	1.5	1.2	1.3	B	Fair to Good
Fluoxetine	0.9	1.0	1.0	C	Fair
Leuprolide	1.1	0.9	1.0	X	Limited to Fair
Salmeterol	1.1	0.8	0.9	C	Limited
Bupropion	0.6	1.0	0.9	C	Limited to Fair
Metformin	1.2	0.6	0.8	B	Fair
Oxycodone	0.9	0.8	0.8	B	Limited
Insulin	1.0	0.7	0.8	B	Fair
Codeine	0.8	0.7	0.8	C	Fair to Good
Metoclopramide	0.8	0.6	0.7	B	Fair to Good
Escitalopram	0.9	0.5	0.7	C	Limited
Montelukast	0.7	0.5	0.6	B	Limited
Chorionic gonadotropin[d]	0.8	0.4	0.6	X	Limited to Fair
Paroxetine	0.3	0.7	0.6	D	Good
Trimethoprim	0.3	0.7	0.5	C	Good
Sulfamethoxazole	0.3	0.7	0.5	C	Limited
Alprazolam	0.6	0.5	0.5	D	Fair to Good

*Varying strengths of the same component were combined. Commonly used was defined as exposure to any component in the first trimester as reported by 0.5% or more of women. Multiple exposures to the same component in the first trimester were counted only once.

** Teratology Information System (TERIS) - The data available on which the risk assessment is based is rated as *None*, *Limited*, *Fair*, *Good*, or *Excellent*. Risk assessments based on evidence that is *Limited* or *Fair* ought to be considered tentative and may change as more information becomes available. Even with *Good* data, only crude estimates of the magnitude of the risk are often possible. Each agent is based on a consensus of ratings by seven internationally-recognized authorities in clinical teratology.

[a] Progestins include desogestrel, etonogestrel (pill and implant), levonorgestrel, medroxyprogesterone, noregelgestromin, norethindrone, norgestimate, NOS-Oral contraceptive, and NOS-Oral contraceptive (progestin only); but excludes drospirenone (progesterone receptor agonist/antagonist) and hydroxyprogesterone.

[b] Estrogenic compounds include ethinyl estradiol, estradiol cypionate and NOS-estrogen.

[c] Follitropin includes follicle-stimulating hormone (FSH), follitropin alpha, and follitropin beta and urofollitropin.

[d] Chorionic gonadotropin includes gonadotropin chorionic and choriogonadotropin alfa.